IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ABBOTT GMBH & CO., KG, ABBOTT BIORESEARCH CENTER, INC. AND ABBOTT BIOTECHNOLOGY LTD.,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 4:09-cv-11340-FDS
CENTOCOR ORTHO BIOTECH, INC. AND CENTOCOR BIOLOGICS, LLC.,	)	
Defendants.	)	

DECLARATION OF DR. MICHAEL J. GRUSBY, PH.D.

I, Dr. Michael Jeffrey Grusby, declare as follows:

Introduction

1. My name is Dr. Michael J. Grusby, Ph.D.

2. I am currently Senior Associate Dean for Academic Affairs and Diversity at the Harvard School of Public Health, and I hold an appointment as Professor of Molecular Immunology in the Department of Immunology and Infectious Diseases. From 1998-2008, I was an Associate Professor of Medicine at Harvard Medical School and an immunologist at Brigham and Women's Hospital in Boston, MA.

3. I hold a Bachelor of Arts degree in biology and chemistry from McDaniel College in Westminster, MD, and a PhD in biochemistry, molecular biology, and cell biology from Northwestern University in Evanston, IL.

4. My area of expertise is signal transduction and development of immune cells called T lymphocytes.

5. I understand that Abbott GmbH & Co., Abbott Bioresearch Center, Inc., and Abbott Biotechnology Ltd. have filed a patent infringement lawsuit against Centocor Ortho Biotech, Inc. and Centocor Biologics, LLC. in the United States District Court for the District of Massachusetts in the above-captioned case. Throughout this declaration, I will use the term “Abbott” to refer to the plaintiffs and “Centocor” to refer to the defendants.

6. I understand that the patents at issue in this litigation are U.S. Patent No. 6,914,128 (the '128 patent) and 7,504,485 (the '485 patent). I have reviewed the specification and claims of these patents and used these as context for considering the meaning of the disputed terms as they would be understood by a person of ordinary skill in the art.

7. It is my understanding that, in the related patent interference proceeding, Abbott defined the person of ordinary skill in the art as of March 25, 1999 as having "a Ph.D. in molecular biology, or similar degree, or equivalent experience and at least three years post-doctoral experience working in the field of antibody engineering technology." I agree with this definition and adopt it for purposes of this declaration. I understand that Centocor has defined a person of ordinary skill as one having "a Ph.D. in microbiology or a similar degree and at least four years of experience making, modifying, and testing antibodies." The differences in these proposed definitions is not significant enough to impact how the claim terms at issue would be interpreted.

8. I have been asked by Abbott to provide this expert declaration in support of Abbott's Claim Construction Brief.

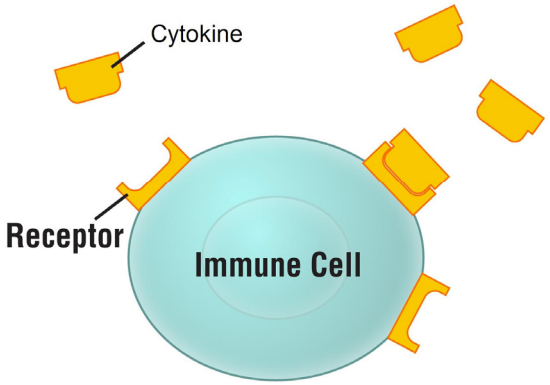
IL-12

9. Our genetic information is encoded as DNA in our cells. The DNA, in turn, holds the blueprints for assembling small molecules called amino acids into larger molecules called proteins. There are 20 amino acids in humans, which can be strung together in nearly infinite variations to make diverse proteins. The order, or sequence, of the amino acids helps to give particular proteins highly specific shapes and sizes.

10. The human immune system coordinates responses to microbial infection and injury, in part, by producing proteins called "cytokines" which transmit signals between immune cells, known generally as "leukocytes." There are dozens of known cytokines, each of which plays a particular role in regulating the human immune system and its responses.

11. Interleukin-12, also known as IL-12, is a type of cytokine which is naturally produced in the human body. IL-12 plays an important role in the immune system's normal response to infection by helping drive the production of certain subsets of immune cells which are necessary for fighting microbes. IL-12 facilitates inter-cellular communication between leukocytes, hence the name "interleukin." IL-12 itself consists of two protein subunits named p35 and p40. As discussed above, each protein subunit, in turn, is made up of chains of amino acids.

12. Cytokines, such as IL-12, exert their effect on cells by binding to specific receptors on the cell surface. The binding of a cytokine to its receptor on the cell triggers a signal within the cell. Depending on which cytokine it is, and further what type of cell, the transmitted signal directs the cell to initiate some type of action, such as cell division, cell maturation, and/or production of other proteins.



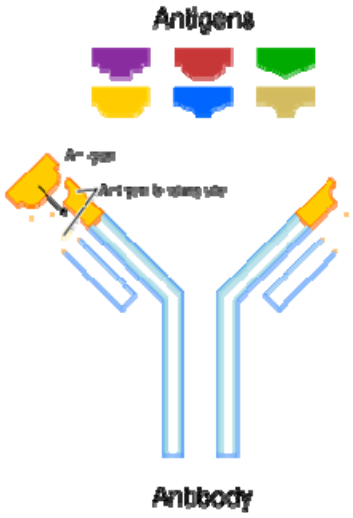
13. Inflammatory responses, when inappropriately triggered or sustained, can cause tissue damage and disease. When the damage is caused by an immune response to a protein or other molecule normally present in one's own body, such inflammation is a type of "auto-immunity", i.e. immunity against the self. IL-12 is known to play a role in some autoimmune diseases, such as rheumatoid arthritis and psoriasis.

Antibodies

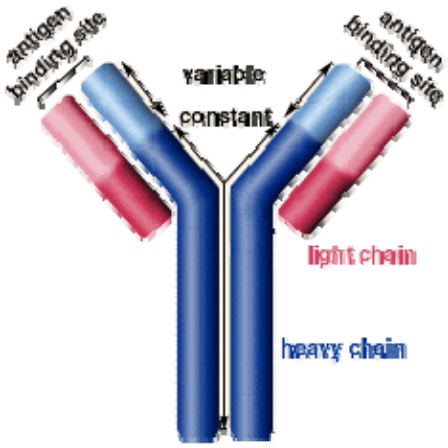
14. One therapeutic strategy for treating autoimmune diseases is to inhibit the effects of IL-12 by using a genetically engineered antibody. An “antibody” is a protein produced by the immune system which specifically targets other proteins, usually those associated with invading microorganisms. Proteins associated with microorganisms trigger the immune system to manufacture antibodies for defense. Proteins that generate a defensive antibody response are known as “antigens”, for antibody-generating. Ordinarily, a naturally-occurring human antibody will not target a human protein from the same individual because it is not “foreign” to the immune system of that individual. The specification and claims of the Abbott patents relate to genetically-engineered human antibodies which are capable of targeting human IL-12.

15. Antibodies target specific antigens by attaching themselves to them in a process called “binding.” Antibodies are highly specific for their target antigens; one antibody will usually bind only to a single antigen, though a single antigen may provoke multiple different antibodies against it. The binding of an antibody to an antigen is highly dependent on the shape of the antibody and the antigen, which must fit together like a lock and key.

16. Antibodies relevant for clinical purposes have a Y-shaped appearance, where the "arms" of the Y shape are responsible for binding to a specific protein target, also known as an "antigen". As shown in the illustration below, binding refers to a lock-and-key fit between the antibody and the antigen, and is dictated by the precise three-dimensional shape of each.



17. Antibodies are made up of protein "chains". The shorter two chains are called "light" chains and the longer two chains are called "heavy" chains. While the antigen binding areas at the tips of the "Y" shape are highly variable between different antibodies, the stem of the Y is substantially similar for all antibodies of a given type. This region is called the "constant" region of an antibody. See illustration below:



Neutralizing Antibodies

18. One protein can have several different biological activities. For example, in the case of a cytokine, such as IL-12, these biological activities include the ability to bind to cytokine receptors on the surface of immune cells, the ability to induce proliferation of immune cells, and the ability to stimulate the production of other secondary cytokines, such as interferon-gamma (discussed below), by immune cells.

19. Only a subset of the antibodies that bind to any given cytokine will have the ability to inhibit one or more of such biological activities, i.e. will be a neutralizing antibody, and there are several ways to test whether, or to what extent, an antibody is a neutralizing antibody.

Proliferation Assays

20. If a cytokine causes proliferation (reproduction) of cells, for example immune cells, it is possible that a subset of antibodies that bind to that cytokine might inhibit the cells' proliferation. A test that can be referred to as a "proliferation assay" can be used to measure whether, or to what extent, an antibody inhibits such cellular proliferation.

21. A proliferation assay that is commonly used to study proliferation of immune cells involves stimulating immune cells called lymphocytes with a plant protein called PHA, also known as "phytohemagglutinin." The PHA stimulates the lymphocytes to mature into cells called "lymphoblasts" or simply "blasts." Lymphocytes stimulated by PHA to mature and proliferate are referred to as "PHA blasts" for short. Certain cytokines, such as IL-2 and IL-12, can further increase the proliferation of PHA blasts. A test that measures the extent to which an antibody can inhibit the proliferation of stimulated PHA blasts is referred to as a PHA assay.

Interferon Gamma Assays

22. Another test that can be used to determine whether an antibody, such as an anti-IL-12 antibody, is a neutralizing antibody is to determine whether it inhibits production of a cytokine called "interferon gamma" (often abbreviated to "IFN-γ") by immune cells.

23. It has been known for some time that certain cytokines can stimulate the production of IFN-γ by immune cells. It has also been known for some time that there are several different ways in which an antibody's ability to inhibit this IFN-γ production can be tested. For example, as described by Wu et al. in 1996 (*See* Gunther Decl. Ex. 7), both resting and activated T and NK cells (types of immune cells) can be induced to produce large amounts of IFN- γ. Thus, although stimulated PHA blasts can be used to test the ability of an antibody to inhibit IFN-γ production, other immune cells may also be used to test inhibition.

24. It has also been known for some time that IFN-γ production can be measured in cells grown in a dish (i.e. in an "in vitro" experiment), or can be measured in blood samples taken from a living organism after administration with a cytokine (i.e. an "*in vivo*" experiment). Thus, the specification of the '128 and '485 patents describes both *in vitro* (Example 3) and *in viv*o (Example 4) tests that can be used to study IFN-γ production.

Receptor Binding Assays

25. Some cytokines, such as IL-12, exert their biological effects in the body by binding to a "receptor" found on the surface of cells. A receptor is a part of the cell surface that is shaped to match up with a particular protein (for example, a cytokine) that will bind to that part of the cell surface, Upon binding of the protein to its receptor, the protein can trigger signals into the cell which gives the cell instructions about what actions to take in response the binding of the protein.

26. Sometimes when an antibody binds to a protein, such as a cytokine, it can prevent the protein from binding to its receptor. Generally, only a subset of the antibodies that bind to any given protein will inhibit the ability of that protein to bind to its receptor.

27. The ability of an antibody to inhibit the binding of a protein to its receptor can be tested using an assay referred to as a receptor binding assay.

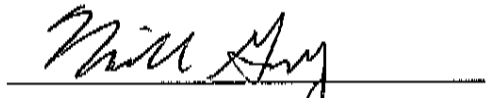
28. It has been known for some time that are several ways to test the ability of an antibody, such as an anti-IL-12 antibody, to inhibit the binding of a cytokine to its receptor. For example, as described by Persky et al. back in 1998 (*See* Gunther Decl. Exhibit 8), cells referred to as "COS-7" cells (a type of monkey kidney cells) that had been artificially engineered to display human IL-12 receptors on their surface were used to show that IL-12 antibodies could inhibit the binding of human IL-12 to human IL-12 receptors. Thus, although stimulated PHA blasts are one type of cells that can be used in an IL-12 receptor binding assay, such cells need not be used.

29. I have reviewed Abbott's and Centocor's proposed claim constructions and considered them in light of the patent specification and claims. To the extent any of the disputed terms require claim construction, I agree with each of the constructions proposed by Abbott. Abbott's proposed constructions are consistent with the patent specification and claims viewed from the perspective of one of ordinary skill in the art at the relevant time. I disagree with Centocor's proposed constructions because each disputed construction attempts to incorporate illustrative examples as a required element of the claim. The person of ordinary skill would not have understood the terms as Centocor has proposed because the additional limitations they propose differ from the common meanings of the words as they would have been understood at the time .

30. I reserve the right to supplement the statements made in this declaration in response to new claim construction arguments or proposals put forth by Centocor subsequent to the filing of this declaration.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on September 10, 2010



Michael J. Grusby, Ph.D.